

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number  
**WO 02/10170 A1**

- (51) International Patent Classification<sup>7</sup>: **C07D 487/04**, A61K 31/495, 31/415, A61P 25/28 // (C07D 487/04, 241:00, 235:00)
- (74) Agent: **THOMPSON, John**; Merck & Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).
- (21) International Application Number: PCT/GB01/03214
- (22) International Filing Date: 18 July 2001 (18.07.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 0018473.9 27 July 2000 (27.07.2000) GB
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): **MERCK SHARP & DOHME LIMITED** [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **GOODACRE, Simon, Charles** [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). **HALLETT, David, James** [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). **STREET, Leslie, Joseph** [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).
- Published:  
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: IMIDAZO-PYRAZINE DERIVATIVES AS LIGANDS FOR GABA RECEPTORS

(57) Abstract: A class of imidazo[1,2- $\alpha$ ]pyrazine analogues substituted in the 3-position by a substituted phenyl ring, being selective ligands for GABA<sub>A</sub> receptors which interact more favourably with the  $\alpha$ 2 and/or  $\alpha$ 3 subunit than with the  $\alpha$ 1 subunit, are accordingly of benefit in the treatment and/or prevention of a variety of disorders of the central nervous system, including anxiety and convulsions, with a reduced propensity to cause sedation.

WO 02/10170 A1

## IMIDAZO-PYRAZINE DERIVATIVES AS LIGANDS FOR GABA RECEPTORS

5       The present invention relates to a class of substituted imidazo-  
pyrazine derivatives and to their use in therapy. More particularly, this  
invention is concerned with imidazo[1,2-*a*]pyrazine analogues which are  
substituted in the 3-position by a substituted phenyl ring. These  
compounds are ligands for GABA<sub>A</sub> receptors and are therefore useful in  
the therapy of deleterious mental states.

10       Receptors for the major inhibitory neurotransmitter, gamma-  
aminobutyric acid (GABA), are divided into two main classes: (1) GABA<sub>A</sub>  
receptors, which are members of the ligand-gated ion channel superfamily;  
and (2) GABA<sub>B</sub> receptors, which may be members of the G-protein linked  
receptor superfamily. Since the first cDNAs encoding individual GABA<sub>A</sub>  
15       receptor subunits were cloned the number of known members of the  
mammalian family has grown to include at least six  $\alpha$  subunits, four  $\beta$   
subunits, three  $\gamma$  subunits, one  $\delta$  subunit, one  $\epsilon$  subunit and two  $\rho$   
subunits.

20       Although knowledge of the diversity of the GABA<sub>A</sub> receptor gene  
family represents a huge step forward in our understanding of this ligand-  
gated ion channel, insight into the extent of subtype diversity is still at an  
early stage. It has been indicated that an  $\alpha$  subunit, a  $\beta$  subunit and a  $\gamma$   
subunit constitute the minimum requirement for forming a fully  
functional GABA<sub>A</sub> receptor expressed by transiently transfecting cDNAs  
25       into cells. As indicated above,  $\delta$ ,  $\epsilon$  and  $\rho$  subunits also exist, but are  
present only to a minor extent in GABA<sub>A</sub> receptor populations.

30       Studies of receptor size and visualisation by electron microscopy  
conclude that, like other members of the ligand-gated ion channel family,  
the native GABA<sub>A</sub> receptor exists in pentameric form. The selection of at  
least one  $\alpha$ , one  $\beta$  and one  $\gamma$  subunit from a repertoire of seventeen allows  
for the possible existence of more than 10,000 pentameric subunit

combinations. Moreover, this calculation overlooks the additional permutations that would be possible if the arrangement of subunits around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

5            Receptor subtype assemblies which do exist include, amongst many others,  $\alpha 1\beta 2\gamma 2$ ,  $\alpha 2\beta \gamma 1$ ,  $\alpha 2\beta 2/3\gamma 2$ ,  $\alpha 3\beta \gamma 2/3$ ,  $\alpha 4\beta \delta$ ,  $\alpha 5\beta 3\gamma 2/3$ ,  $\alpha 6\beta \gamma 2$  and  $\alpha 6\beta \delta$ . Subtype assemblies containing an  $\alpha 1$  subunit are present in most areas of the brain and are thought to account for over 40% of GABA<sub>A</sub> receptors in the rat. Subtype assemblies containing  $\alpha 2$  and  $\alpha 3$  subunits respectively  
10           are thought to account for about 25% and 17% of GABA<sub>A</sub> receptors in the rat. Subtype assemblies containing an  $\alpha 5$  subunit are expressed predominantly in the hippocampus and cortex and are thought to represent about 4% of GABA<sub>A</sub> receptors in the rat.

             A characteristic property of all known GABA<sub>A</sub> receptors is the  
15           presence of a number of modulatory sites, one of which is the benzodiazepine (BZ) binding site. The BZ binding site is the most explored of the GABA<sub>A</sub> receptor modulatory sites, and is the site through which anxiolytic drugs such as diazepam and temazepam exert their effect. Before the cloning of the GABA<sub>A</sub> receptor gene family, the benzodiazepine  
20           binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been shown to be pharmacologically equivalent to a GABA<sub>A</sub> receptor comprising the  $\alpha 1$  subunit in combination with a  $\beta$  subunit and  $\gamma 2$ . This is the most abundant GABA<sub>A</sub> receptor subtype, and is believed to represent almost  
25           half of all GABA<sub>A</sub> receptors in the brain.

             Two other major populations are the  $\alpha 2\beta \gamma 2$  and  $\alpha 3\beta \gamma 2/3$  subtypes. Together these constitute approximately a further 35% of the total GABA<sub>A</sub> receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand  
30           binding, although the BZ2 subtype may also include certain  $\alpha 5$ -containing subtype assemblies. The physiological role of these subtypes has hitherto

been unclear because no sufficiently selective agonists or antagonists were known.

It is now believed that agents acting as BZ agonists at  $\alpha 1\beta\gamma 2$ ,  $\alpha 2\beta\gamma 2$  or  $\alpha 3\beta\gamma 2$  subunits will possess desirable anxiolytic properties. Compounds which are modulators of the benzodiazepine binding site of the GABA<sub>A</sub> receptor by acting as BZ agonists are referred to hereinafter as "GABA<sub>A</sub> receptor agonists". The  $\alpha 1$ -selective GABA<sub>A</sub> receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through GABA<sub>A</sub> receptors containing the  $\alpha 1$  subunit. Accordingly, it is considered that GABA<sub>A</sub> receptor agonists which interact more favourably with the  $\alpha 2$  and/or  $\alpha 3$  subunit than with  $\alpha 1$  will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Also, agents which are antagonists or inverse agonists at  $\alpha 1$  might be employed to reverse sedation or hypnosis caused by  $\alpha 1$  agonists.

The compounds of the present invention, being selective ligands for GABA<sub>A</sub> receptors, are therefore of use in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine; depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder; psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; attention deficit hyperactivity disorder; speech disorders, including stuttering; and disorders of circadian rhythm, e.g. in subjects suffering from the effects of jet lag or shift work.

Further disorders for which selective ligands for GABA<sub>A</sub> receptors may be of benefit include pain and nociception; emesis, including acute, delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation, as well as motion sickness, and post-operative  
5 nausea and vomiting; eating disorders including anorexia nervosa and bulimia nervosa; premenstrual syndrome; muscle spasm or spasticity, e.g. in paraplegic patients; hearing disorders, including tinnitus and age-related hearing impairment; urinary incontinence; and the effects of substance abuse or dependency, including alcohol withdrawal. Selective  
10 ligands for GABA<sub>A</sub> receptors may also be effective as pre-medication prior to anaesthesia or minor procedures such as endoscopy, including gastric endoscopy.

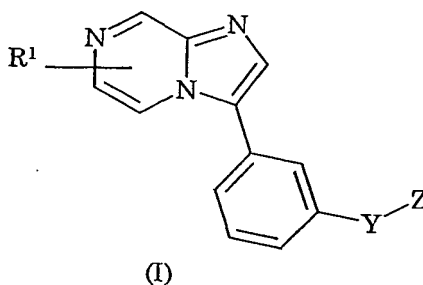
The present invention provides a class of imidazo-pyrazine derivatives which possess desirable binding properties at various GABA<sub>A</sub>  
15 receptor subtypes. The compounds in accordance with the present invention have good affinity as ligands for the  $\alpha 2$  and/or  $\alpha 3$  subunit of the human GABA<sub>A</sub> receptor. The compounds of this invention may interact more favourably with the  $\alpha 2$  and/or  $\alpha 3$  subunit than with the  $\alpha 1$  subunit. Desirably, the compounds of the invention will exhibit functional  
20 selectivity in terms of a selective efficacy for the  $\alpha 2$  and/or  $\alpha 3$  subunit relative to the  $\alpha 1$  subunit.

The compounds of the present invention are GABA<sub>A</sub> receptor subtype ligands having a binding affinity ( $K_i$ ) for the  $\alpha 2$  and/or  $\alpha 3$  subunit, as measured in the assay described hereinbelow, of 200 nM or less,  
25 typically of 100 nM or less, and ideally of 20 nM or less. The compounds in accordance with this invention may possess at least a 2-fold, suitably at least a 5-fold, and advantageously at least a 10-fold, selective affinity for the  $\alpha 2$  and/or  $\alpha 3$  subunit relative to the  $\alpha 1$  subunit. However, compounds which are not selective in terms of their binding affinity for the  $\alpha 2$  and/or  
30  $\alpha 3$  subunit relative to the  $\alpha 1$  subunit are also encompassed within the scope of the present invention; such compounds will desirably exhibit

functional selectivity in terms of a selective efficacy for the  $\alpha 2$  and/or  $\alpha 3$  subunit relative to the  $\alpha 1$  subunit.

The present invention provides a compound of formula I, or a salt or prodrug thereof:

5



wherein

Y represents a chemical bond, an oxygen atom, or a -NH- linkage;  
Z represents an optionally substituted aryl or heteroaryl group;  
R<sup>1</sup> represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -OR<sup>a</sup>, -SR<sup>a</sup>, -SOR<sup>a</sup>, -SO<sub>2</sub>R<sup>a</sup>, -SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>COR<sup>b</sup>, -NR<sup>a</sup>CO<sub>2</sub>R<sup>b</sup>, -COR<sup>a</sup>, -CO<sub>2</sub>R<sup>a</sup>, -CONR<sup>a</sup>R<sup>b</sup> or -CR<sup>a</sup>=NOR<sup>b</sup>; and

R<sup>a</sup> and R<sup>b</sup> independently represent hydrogen, hydrocarbon or a heterocyclic group.

The aryl or heteroaryl group Z in the compounds of formula I above may be unsubstituted, or substituted by one or more substituents.

Typically, the group Z will be unsubstituted, or substituted by one or two substituents. Suitably, the group Z is unsubstituted or monosubstituted. Typical substituents on the group Z include halogen, cyano, nitro, amino, formyl, C<sub>2-6</sub> alkoxy carbonyl and -CR<sup>a</sup>=NOR<sup>b</sup>.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable

salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl(C<sub>1-6</sub>)alkyl, indanyl, aryl and aryl(C<sub>1-6</sub>)alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C<sub>3-7</sub> heterocycloalkyl, C<sub>3-7</sub> heterocycloalkyl(C<sub>1-6</sub>)alkyl, heteroaryl and heteroaryl(C<sub>1-6</sub>)alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *tert*-butyl and 2,2-dimethylpropyl. Derived expressions such as "C<sub>1-6</sub> alkoxy", "C<sub>1-6</sub> alkylamino" and "C<sub>1-6</sub> alkylsulphonyl" are to be construed accordingly.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl and dimethylallyl groups.

5        Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

10       Typical examples of C<sub>3-7</sub> cycloalkyl(C<sub>1-6</sub>)alkyl groups include cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl.

Particular indanyl groups include indan-1-yl and indan-2-yl.

Particular aryl groups include phenyl and naphthyl.

Particular aryl(C<sub>1-6</sub>)alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

15       Suitable heterocycloalkyl groups include azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl groups.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, 20       oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C<sub>1-6</sub>)alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl; 25       imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl and isoquinolinylmethyl.

30       The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C<sub>1-6</sub> alkyl, adamantyl, phenyl, halogen, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> aminoalkyl, trifluoromethyl, hydroxy,



C<sub>1-6</sub> alkoxy, aryloxy, keto, C<sub>1-3</sub> alkylenedioxy, nitro, cyano, carboxy, C<sub>2-6</sub> alkoxy carbonyl, C<sub>2-6</sub> alkoxy carbonyl(C<sub>1-6</sub>)alkyl, C<sub>2-6</sub> alkyl carbonyloxy, aryl carbonyloxy, aminocarbonyloxy, C<sub>2-6</sub> alkyl carbonyl, aryl carbonyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulphinyl, C<sub>1-6</sub> alkylsulphonyl, arylsulphonyl, -NR<sup>v</sup>R<sup>w</sup>,  
5 -NR<sup>v</sup>COR<sup>w</sup>, -NR<sup>v</sup>CO<sub>2</sub>R<sup>w</sup>, -NR<sup>v</sup>SO<sub>2</sub>R<sup>w</sup>, -CH<sub>2</sub>NR<sup>v</sup>SO<sub>2</sub>R<sup>w</sup>, -NHCONR<sup>v</sup>R<sup>w</sup>,  
-CONR<sup>v</sup>R<sup>w</sup>, -SO<sub>2</sub>NR<sup>v</sup>R<sup>w</sup> and -CH<sub>2</sub>SO<sub>2</sub>NR<sup>v</sup>R<sup>w</sup>, in which R<sup>v</sup> and R<sup>w</sup> independently represent hydrogen, C<sub>1-6</sub> alkyl, aryl or aryl(C<sub>1-6</sub>)alkyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluoro or chloro.

10 The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug  
15 derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric  
20 centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

In a preferred embodiment, Y represents a chemical bond.

In another embodiment, Y represents an oxygen atom.

25 In a further embodiment, Y represents a -NH- linkage.

Representative values for the substituent Z include phenyl, pyridinyl, thienyl and thiazolyl, any of which groups may be optionally substituted. In a favoured embodiment, Z represents an optionally substituted phenyl group, in particular monosubstituted phenyl.

Examples of typical substituents on the group Z include chloro, cyano, nitro, amino, formyl, methoxycarbonyl and -CH=NOH. Additionally, Z may be substituted by fluoro.

Specific values of Z include cyanophenyl, nitrophenyl, pyridinyl, (amino)(chloro)pyridinyl, cyano-thienyl, formyl-thienyl, methoxycarbonyl-thienyl, thienyl-CH=NOH and thiazolyl. Additionally, Z may represent (cyano)(fluoro)phenyl.

A particular value of Z is cyanophenyl, especially 2-cyanophenyl.

Suitably, R<sup>1</sup> represents hydrogen, hydrocarbon, a heterocyclic group, halogen, trifluoromethyl, -OR<sup>a</sup>, -COR<sup>a</sup>, -CO<sub>2</sub>R<sup>a</sup> or -CR<sup>a</sup>=NOR<sup>b</sup>.

Typical values of R<sup>a</sup> include hydrogen and C<sub>1-6</sub> alkyl. Suitably, R<sup>a</sup> represents hydrogen or methyl.

Typical values of R<sup>b</sup> include hydrogen, C<sub>1-6</sub> alkyl, hydroxy(C<sub>1-6</sub>)alkyl and di(C<sub>1-6</sub>)alkylamino(C<sub>1-6</sub>)alkyl. Suitably, R<sup>b</sup> represents hydrogen, methyl, ethyl, hydroxyethyl or dimethylaminoethyl. Particular values of R<sup>b</sup> include hydrogen, hydroxyethyl and dimethylaminoethyl.

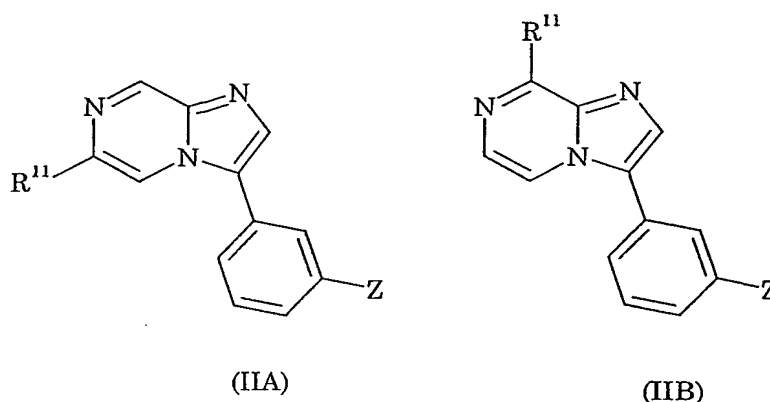
Illustrative values of R<sup>1</sup> include hydrogen, C<sub>1-6</sub> alkyl, hydroxy(C<sub>1-6</sub>)alkyl, heteroaryl, halogen, trifluoromethyl, C<sub>1-6</sub> alkoxy, formyl, C<sub>2-6</sub> alkylcarbonyl, C<sub>2-6</sub> alkoxycarbonyl and -CR<sup>a</sup>=NOR<sup>b</sup>, in which R<sup>a</sup> and R<sup>b</sup> are as defined above.

Specific values of R<sup>1</sup> include hydrogen, methyl, hydroxymethyl, hydroxyethyl, furyl, fluoro, trifluoromethyl, methoxy, formyl, acetyl, methoxycarbonyl and -CR<sup>2</sup>=NOR<sup>3</sup>, in which R<sup>2</sup> represents hydrogen or methyl, and R<sup>3</sup> represents hydrogen, hydroxyethyl or dimethylaminoethyl. Additionally, R<sup>1</sup> may represent hydroxypropyl.

A particular value of R<sup>1</sup> is hydrogen.

R<sup>1</sup> is preferably in the 6- or the 8-position, most preferably the 6-position.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA and IIB, and salts and prodrugs thereof:



wherein

Z is as defined above;

5  $R^{11}$  represents hydrogen,  $C_{1-6}$  alkyl, hydroxy( $C_{1-6}$ )alkyl, heteroaryl, halogen, trifluoromethyl,  $C_{1-6}$  alkoxy, formyl,  $C_{2-6}$  alkylcarbonyl,  $C_{2-6}$  alkoxycarbonyl or  $-CR^4=NOR^5$ ;

$R^4$  represents hydrogen or  $C_{1-6}$  alkyl; and

$R^5$  represents hydrogen,  $C_{1-6}$  alkyl, hydroxy( $C_{1-6}$ )alkyl or  
10 di( $C_{1-6}$ )alkylamino( $C_{1-6}$ )alkyl.

Suitably,  $R^4$  represents hydrogen or methyl.

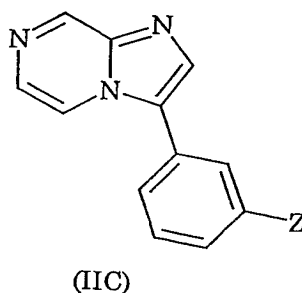
Suitably,  $R^5$  represents hydrogen, methyl, ethyl, hydroxyethyl or dimethylaminoethyl. Particular values of  $R^5$  include hydrogen, hydroxyethyl and dimethylaminoethyl.

15 Where  $R^{11}$  represents heteroaryl, this group is suitably furyl.

Representative values of  $R^{11}$  include hydrogen, methyl, hydroxymethyl, hydroxyethyl, furyl, fluoro, trifluoromethyl, methoxy, formyl, acetyl, methoxycarbonyl and  $-CR^2=NOR^3$ , in which  $R^2$  and  $R^3$  are as defined above. Additionally,  $R^{11}$  may represent hydroxypropyl.

20 A particular value of  $R^{11}$  is hydrogen.

One representative subset of the compounds of formula IIA and IIB above is represented by the compounds of formula IIC, and salts and prodrugs thereof:



wherein Z is as defined above.

In a specific example of a compound of formula IIC, Z represents 2-  
5 cyanophenyl.

Specific compounds within the scope of the present invention include:

3'-(imidazo[1,2-*a*]pyrazin-3-yl)biphenyl-2-carbonitrile;  
and salts and prodrugs thereof.

10 Also provided by the present invention is a method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof or a prodrug thereof.

15 Further provided by the present invention is a method for the treatment and/or prevention of convulsions (e.g. in a patient suffering from epilepsy or a related disorder) which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof or a  
20 prodrug thereof.

The binding affinity ( $K_i$ ) of the compounds according to the present invention for the  $\alpha 3$  subunit of the human GABA<sub>A</sub> receptor is conveniently as measured in the assay described hereinbelow. The  $\alpha 3$  subunit binding affinity ( $K_i$ ) of the compounds of the invention is ideally 50 nM or less,  
25 preferably 20 nM or less.

The compounds according to the present invention will ideally elicit at least a 40%, preferably at least a 50%, and more preferably at least a 60%, potentiation of the GABA EC<sub>20</sub> response in stably transfected recombinant cell lines expressing the  $\alpha 3$  subunit of the human GABA<sub>A</sub> receptor. Moreover, the compounds of the invention will ideally elicit at most a 30%, preferably at most a 20%, and more preferably at most a 10%, potentiation of the GABA EC<sub>20</sub> response in stably transfected recombinant cell lines expressing the  $\alpha 1$  subunit of the human GABA<sub>A</sub> receptor.

The potentiation of the GABA EC<sub>20</sub> response in stably transfected cell lines expressing the  $\alpha 3$  and  $\alpha 1$  subunits of the human GABA<sub>A</sub> receptor can conveniently be measured by procedures analogous to the protocol described in Wafford *et al.*, *Mol. Pharmacol.*, 1996, 50, 670-678. The procedure will suitably be carried out utilising cultures of stably transfected eukaryotic cells, typically of stably transfected mouse Ltk<sup>-</sup> fibroblast cells.

The compounds according to the present invention exhibit anxiolytic activity, as may be demonstrated by a positive response in the elevated plus maze and conditioned suppression of drinking tests (cf. Dawson *et al.*, *Psychopharmacology*, 1995, 121, 109-117). Moreover, the compounds of the invention are substantially non-sedating, as may be confirmed by an appropriate result obtained from the response sensitivity (chain-pulling) test (cf. Bayley *et al.*, *J. Psychopharmacol.*, 1996, 10, 206-213).

The compounds according to the present invention may also exhibit anticonvulsant activity. This can be demonstrated by the ability to block pentylenetetrazole-induced seizures in rats and mice, following a protocol analogous to that described by Bristow *et al.* in *J. Pharmacol. Exp. Ther.*, 1996, 279, 492-501.

In order to elicit their behavioural effects, the compounds of the invention will ideally be brain-penetrant; in other words, these compounds will be capable of crossing the so-called "blood-brain barrier". Preferably,

the compounds of the invention will be capable of exerting their beneficial therapeutic action following administration by the oral route.

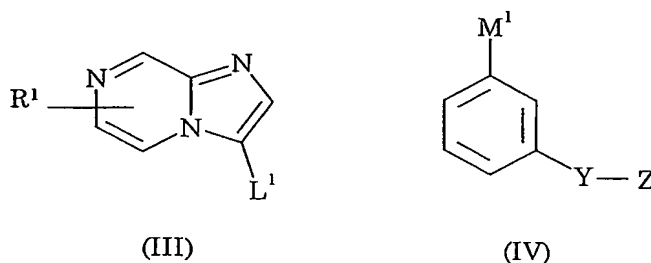
The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner

component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

5           The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar  
10           pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

          In the treatment of anxiety, a suitable dosage level is about 0.01 to  
15           250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

          The compounds in accordance with the present invention may be prepared by a process which comprises reacting a compound of formula III  
20           with a compound of formula IV:



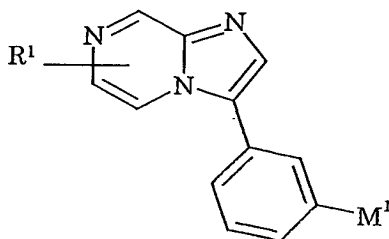
          wherein Y, Z and R¹ are as defined above, L¹ represents a suitable leaving  
25           group, and M¹ represents a boronic acid moiety -B(OH)₂ or a cyclic ester thereof formed with an organic diol, e.g. pinacol, or M¹ represents

-Sn(Alk)<sub>3</sub> in which Alk represents a C<sub>1-6</sub> alkyl group, typically *n*-butyl; in the presence of a transition metal catalyst.

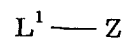
The leaving group L<sup>1</sup> is typically a halogen atom, e.g. bromo.

The transition metal catalyst of use in the reaction between  
5 compounds III and IV is suitably tetrakis(triphenylphosphine)-  
palladium(0). The reaction is conveniently carried out at an elevated  
temperature in a solvent such as *N,N*-dimethylacetamide, advantageously  
in the presence of potassium phosphate.

In an alternative procedure, the compounds according to the present  
10 invention in which Y represents a chemical bond may be prepared by a  
process which comprises reacting a compound of formula V with a  
compound of formula VI:



(V)



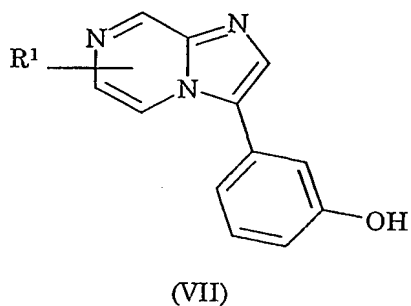
(VI)

15

wherein Z, R<sup>1</sup>, L<sup>1</sup> and M<sup>1</sup> are as defined above; in the presence of a  
transition metal catalyst; under conditions analogous to those described  
above for the reaction between compounds III and IV.

In another procedure, the compounds according to the present  
20 invention in which Y represents an oxygen atom may be prepared by a  
process which comprises reacting a compound of formula VI as defined  
above with a compound of formula VII:

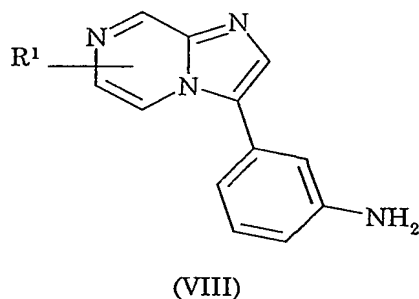




wherein  $R^1$  is as defined above.

The reaction is conveniently carried out under basic conditions, e.g. using sodium hydride in a solvent such as *N,N*-dimethylformamide, typically at an elevated temperature which may be in the region of 120°C.

In a further procedure, the compounds according to the present invention in which Y represents a -NH- linkage may be prepared by a process which comprises reacting a compound of formula VI as defined above with a compound of formula VIII:



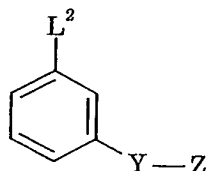
wherein  $R^1$  is as defined above.

In relation to the reaction between compounds VI and VIII, the leaving group  $L^1$  in the compounds of formula VI may suitably represent fluoro.

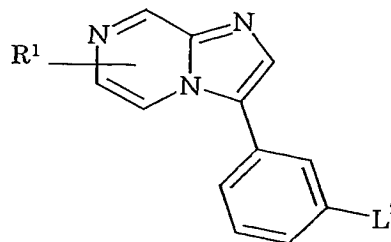
The reaction between compounds VI and VIII is conveniently carried out by heating the reactants, typically at a temperature in the region of 120°C, in a solvent such as *N,N*-dimethylformamide.

Where  $M^1$  in the intermediates of formula IV and V above represents a cyclic ester of a boronic acid moiety  $-B(OH)_2$  formed with pinacol, the relevant compound IV or V may be prepared by reacting bis(pinacolato)diboron with a compound of formula IVA or VA:

5



(IVA)



(VA)

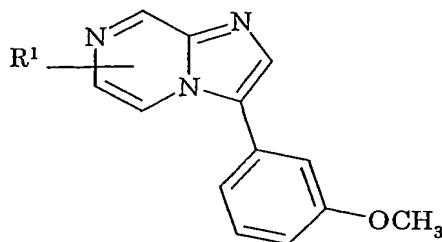
wherein Y, Z and  $R^1$  are as defined above, and  $L^2$  represents hydroxy or a suitable leaving group; in the presence of a transition metal catalyst.

10 Where  $L^2$  represents a leaving group, this is typically trifluoromethanesulphonyloxy (triflyloxy).

The transition metal catalyst of use in the reaction between bis(pinacolato)diboron and compound IVA or VA is suitably dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II). The reaction is  
15 conveniently carried out at an elevated temperature in a solvent such as 1,4-dioxane, typically in the presence of 1,1'-bis(diphenylphosphino)-ferrocene and/or potassium acetate.

Where  $L^2$  in the intermediates of formula VA above represents triflyloxy, the relevant compound VA may be prepared by reacting the  
20 appropriate compound of formula VII as defined above with triflic anhydride, typically in the presence of pyridine. Analogous conditions may be utilised for converting an intermediate of formula IVA above wherein  $L^2$  represents hydroxy into the corresponding compound wherein  $L^2$  represents triflyloxy.

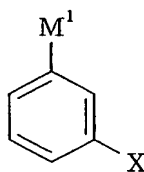
25 The intermediates of formula VII above may suitably be prepared from the appropriate methoxy-substituted precursor of formula IX:



(IX)

wherein R<sup>1</sup> is as defined above; by treatment with hydrogen bromide,  
5 typically in acetic acid at reflux.

The intermediates of formula VIII and IX above may be prepared by reacting a compound of formula III as defined above with the appropriate compound of formula X:

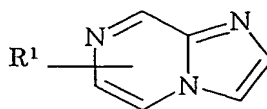


(X)

10

wherein M<sup>1</sup> is as defined above, and X represents amino or methoxy; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

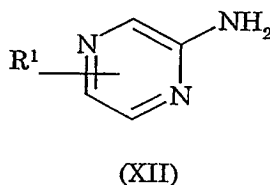
15 Where L<sup>1</sup> in the intermediates of formula III above represents bromo, this compound may be prepared by bromination of the corresponding compound of formula XI:



(XI)

wherein R<sup>1</sup> is as defined above; typically by treatment with bromine in methanol, in the presence of sodium acetate and optionally also potassium bromide.

- 5           The intermediates of formula XI may be prepared by reacting chloroacetaldehyde with the requisite compound of formula XII:

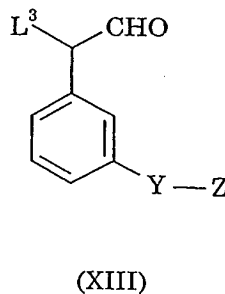


- 10          wherein R<sup>1</sup> is as defined above.

The reaction is conveniently carried out by heating the reactants under basic conditions in a suitable solvent, e.g. sodium hydrogencarbonate in a lower alkanol such as methanol and/or ethanol at the reflux temperature of the solvent.

- 15           Alternatively, the compound of formula XII may be reacted with bromoacetaldehyde dimethylacetal in the presence of 48% HBr in refluxing ethanol to form an intermediate of formula XI.

- 20           In a still further procedure, the compounds according to the present invention may be prepared by a process which comprises reacting a compound of formula XII as defined above with a compound of formula XIII:

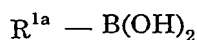


wherein Y and Z are as defined above, and L<sup>3</sup> represents a suitable leaving group; under conditions analogous to those described above for the reaction between chloroacetaldehyde and compound XII.

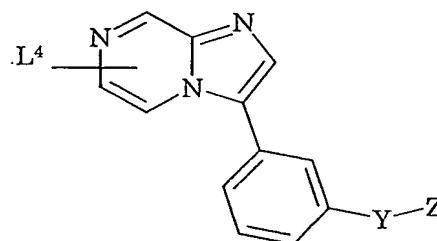
5           The leaving group L<sup>3</sup> is suitably a halogen atom, e.g. bromo.

In a yet further procedure, the compounds according to the present invention wherein R<sup>1</sup> represents an aryl or heteroaryl moiety may be prepared by a process which comprises reacting a compound of formula XIV with a compound of formula XV:

10



(XIV)



(XV)

wherein Y and Z are as defined above, R<sup>1a</sup> represents an aryl or heteroaryl moiety, and L<sup>4</sup> represents a suitable leaving group; in the presence of a transition metal catalyst.

15

The leaving group L<sup>4</sup> is typically a halogen atom, e.g. chloro.

The transition metal catalyst of use in the reaction between compounds XIV and XV is suitably tris(dibenzylideneacetone)-dipalladium(0), in which case the reaction is conveniently effected at an elevated temperature in a solvent such as 1,4-dioxane, typically in the presence of tri-*tert*-butylphosphine and cesium carbonate.

20

Where L<sup>4</sup> in the compounds of formula XV above represents a halogen atom, these compounds correspond to compounds of formula I as defined above wherein R<sup>1</sup> represents halogen, and they may therefore be prepared by any of the methods described above for the preparation of the compounds according to the invention.

25

Where they are not commercially available, the starting materials of formula IV, VI, X, XII, XIII and XIV may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

5           It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I wherein  $R^1$  represents  $C_{1-6}$  alkoxy carbonyl initially obtained may be  
10 reduced with lithium aluminium hydride to the corresponding compound of formula I wherein  $R^1$  represents hydroxymethyl. The latter compound may then be oxidised to the corresponding compound of formula I wherein  $R^1$  represents formyl by treatment with manganese dioxide. The formyl derivative thereby obtained may be condensed with a hydroxylamine  
15 derivative of formula  $H_2N-OR^b$  to provide a compound of formula I wherein  $R^1$  represents  $-CH=NOR^b$ . Alternatively, the compound of formula I wherein  $R^1$  represents formyl may be reacted with a Grignard reagent of formula  $R^aMgBr$  to afford a compound of formula I wherein  $R^1$  represents  $-CH(OH)R^a$ , and this compound may in turn be oxidised using manganese  
20 dioxide to the corresponding compound of formula I wherein  $R^1$  represents  $-COR^a$ . The latter compound may then be condensed with a hydroxylamine derivative of formula  $H_2N-OR^b$  to provide a compound of formula I wherein  $R^1$  represents  $-CR^a=NOR^b$ .

Where the above-described processes for the preparation of the  
25 compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds  
30 may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of

diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Example illustrates the preparation of compounds according to the invention.

The compounds in accordance with this invention potentially inhibit the binding of [<sup>3</sup>H]-flumazenil to the benzodiazepine binding site of human GABA<sub>A</sub> receptors containing the  $\alpha 2$  or  $\alpha 3$  subunit stably expressed in Ltk-cells.

#### *Reagents*

- Phosphate buffered saline (PBS).
- Assay buffer: 10 mM KH<sub>2</sub>PO<sub>4</sub>, 100 mM KCl, pH 7.4 at room temperature.
- [<sup>3</sup>H]-Flumazenil (18 nM for  $\alpha 1\beta 3\gamma 2$  cells; 18 nM for  $\alpha 2\beta 3\gamma 2$  cells; 10 nM for  $\alpha 3\beta 3\gamma 2$  cells) in assay buffer.
- Flunitrazepam 100  $\mu$ M in assay buffer.
- Cells resuspended in assay buffer (1 tray to 10 ml).

#### 30 *Harvesting Cells*

Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of the cells are removed. The cells are pelleted by centrifuging for 20 min at 3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

#### Assay

- Can be carried out in deep 96-well plates or in tubes. Each tube contains:
- 300  $\mu$ l of assay buffer.
  - 50  $\mu$ l of [ $^3$ H]-flumazenil (final concentration for  $\alpha 1\beta 3\gamma 2$ : 1.8 nM; for  $\alpha 2\beta 3\gamma 2$ : 1.8 nM; for  $\alpha 3\beta 3\gamma 2$ : 1.0 nM).
  - 50  $\mu$ l of buffer or solvent carrier (e.g. 10% DMSO) if compounds are dissolved in 10% DMSO (total); test compound or flunitrazepam (to determine non-specific binding), 10  $\mu$ M final concentration.
  - 100  $\mu$ l of cells.

Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000 dpm for total counts and less than 200 dpm for non-specific binding if using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid scintillant. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant  $K_i$  can be calculated for each test compound.

The compound of the accompanying Example was tested in the above assay, and was found to possess a  $K_i$  value for displacement of [ $^3$ H]-flumazenil from the  $\alpha 2$  and/or  $\alpha 3$  subunit of the human GABA<sub>A</sub> receptor of 100 nM or less.



### EXAMPLE 1

#### 3'-(Imidazo[1,2-*a*]pyrazin-3-yl)biphenyl-2-carbonitrile

- 5           A mixture of 2-bromobenzonitrile (9.1 g, 50 mmol), 3-aminobenzeneboronic acid monohydrate (11.6 g, 75 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.73 g, 1.5 mmol) in dimethoxyethane (50 ml) and 2M sodium carbonate solution (25 ml) was heated at 80°C for 20 h. After cooling to ambient temperature the reaction
- 10           was partitioned between ethyl acetate (400 ml) and water (400 ml). The organics were washed with brine (400 ml), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with isohexane on a gradient of ethyl acetate (0-25%) gave 3'-aminobiphenyl-2-carbonitrile as a colourless
- 15           oil that solidified on standing to afford a white solid (9.5 g, 98%):  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 3.79 (2H, br), 6.75 (1H, ddd, *J* 8, 3 and 1), 6.84 (1H, dd, *J* 3 and 3), 6.92 (1H, dd, *J* 8 and 3), 7.25 (1H, dd, *J* 8 and 8), 7.40 (1H, ddd, *J* 8, 8 and 1), 7.50 (1H, dd, *J* 8 and 1), 7.62 (1H, ddd, *J* 8, 8 and 1), 7.73 (1H, dd, *J* 8 and 1).
- 20           A solution of 3'-aminobiphenyl-2-carbonitrile (10.9 g, 56 mmol) in 1,4-dioxane (30 ml) was treated with a solution of 25% aqueous sulfuric acid (150 ml). The resulting suspension was cooled to 0°C before being treated dropwise over 10 minutes with a solution of sodium nitrite (4.6 g, 67 mmol) in water (10 ml). After stirring at 0°C for 30 minutes the
- 25           reaction was poured into hot (70°C) water (500 ml). On cooling to ambient temperature the product was extracted into ethyl acetate (500 ml), the organics were washed with water (300 ml), brine (300 ml) and dried over anhydrous sodium sulfate. Filtration and concentration *in vacuo* afforded 3'-hydroxybiphenyl-2-carbonitrile as a dark oil (7.1 g, 65%):  $\delta_{\text{H}}$  (400 MHz,
- 30           CDCl<sub>3</sub>) 5.40 (1H, br), 6.92 (1H, ddd, *J* 8, 3 and 1), 7.04 (1H, dd, *J* 3 and 3), 7.11 (1H, ddd, *J* 8, 3 and 1), 7.35 (1H, dd, *J* 8 and 8), 7.44 (1H, ddd, *J* 8, 8 and 1), 7.50 (1H, dd, *J* 8 and 1), 7.62 (1H, ddd, *J* 8, 8 and 1), 7.73 (1H, dd, *J* 8 and 1).

and 1), 7.51 (1H, dd, *J* 8 and 1), 7.64 (1H, ddd, *J* 8, 8 and 1), 7.75 (1H, dd, *J* 8 and 1).

3'-Hydroxybiphenyl-2-carbonitrile (0.48 g, 2.47 mmol) and dry pyridine (0.98 g, 12.35 mmol) were dissolved in dichloromethane (7 ml) and cooled to 0°C before dropwise addition of trifluoromethanesulfonic anhydride (1.04 g, 3.70 mmol) over 5 min. The mixture was stirred at 0°C for 10 min and then at 25°C for 1 h. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate (200 ml) and water (150 ml). The organic layer was washed with brine (150 ml), dried over anhydrous sodium sulfate and evaporated to give a brown oil. Purification by silica gel chromatography eluting with isohexane on a gradient of ethyl acetate (0-30%) gave *trifluoromethanesulfonic acid 2'-cyanobiphenyl-3-yl ester* as a yellow oil (544 mg, 67%):  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.37 (1H, ddd, *J* 8, 3 and 1), 7.39 (1H, dd, *J* 3 and 3), 7.50-7.60 (2H, m), 7.61-7.65 (2H, m), 7.64 (1H, td, *J* 8 and 1), 7.80 (1H, dd, *J* 8 and 1).

Trifluoromethanesulfonic acid 2'-cyanobiphenyl-3-yl ester (0.55 g, 1.66 mmol), potassium acetate (0.49 g, 4.98 mmol) and bis(pinacolato)diboron (0.55 g, 2.16 mmol) were dissolved in 1,4-dioxane (10 ml) and the mixture degassed with  $\text{N}_2$  for 15 min. Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (41 mg, 0.05 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (28 mg, 0.05 mmol) were then added and the mixture heated at 85°C for 18 h. The mixture was cooled to ambient temperature and partitioned between ethyl acetate (150 ml) and water (50 ml). The organic layer was washed with brine (50 ml), dried over anhydrous sodium sulfate and evaporated *in vacuo* to give *3'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)biphenyl-2-carbonitrile* as a black oil (0.51 g, 100%). This oil was dissolved in sufficient *N,N*-dimethylacetamide to give a 0.5M stock solution.

2-Aminopyrazine (100 mg, 1.1 mmol) and bromoacetaldehyde dimethylacetal (253 mg, 1.6 mmol) were dissolved in ethanol (4.5 ml), hydrobromic acid (48%, 0.5 ml) added and the mixture was heated under

reflux for 18 h. The solution was allowed to cool to room temperature then pre-adsorbed directly onto silica. Purification by silica gel chromatography eluting with dichloromethane and 1% conc. ammonia on a gradient of methanol (1-4%) gave *imidazo[1,2-*a*]pyrazine* (90 mg, 72%) as a white crystalline solid:  $\delta_{\text{H}}$  (360 MHz,  $\text{CDCl}_3$ ) 6.70 (1H, s), 7.82 (1H, s), 7.88 (1H, d, *J* 4), 8.29 (1H, d, *J* 4), 9.12 (1H, s).

Imidazo[1,2-*a*]pyrazine (90 mg, 0.76 mmol) and sodium acetate (75 mg, 0.91 mmol) were dissolved in methanol (2 ml) saturated with potassium bromide and cooled to  $-10^\circ\text{C}$  before dropwise addition of bromine (121 mg, 0.76 mmol) over 5 min. On complete addition the mixture was quenched by addition of 1N sodium sulfite solution (2 ml) and the solvent removed *in vacuo*. The residue was dissolved in water (15 ml) and saturated sodium hydrogencarbonate solution (15 ml) and extracted with ethyl acetate (2 x 40 ml). The organics were combined then washed with brine (40 ml), dried over anhydrous sodium sulfate and evaporated to give *3-bromoimidazo[1,2-*a*]pyrazine* (150 mg, 100%) as a white crystalline solid:  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.80 (1H, s), 6.87 (1H, d, *J* 7), 7.71 (1H, s), 8.27 (1H, d, *J* 7).

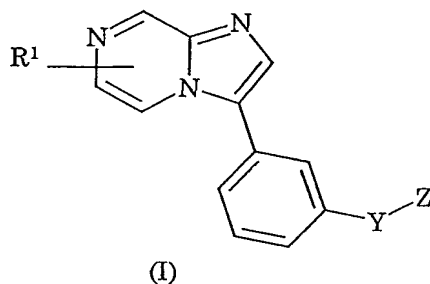
A mixture of *3-bromoimidazo[1,2-*a*]pyrazine* (150 mg, 0.76 mmol), potassium phosphate (321 mg, 1.51 mmol) and 3'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)biphenyl-2-carbonitrile (3 ml of a 0.5M solution in *N,N*-dimethylacetamide) were degassed with  $\text{N}_2$  for 15 min. Tetrakis(triphenylphosphine)palladium(0) (44 mg, 0.04 mmol) was added and the mixture heated at  $80^\circ\text{C}$  for 18 h. The reaction was allowed to cool to room temperature, diluted with water (20 ml) and saturated sodium hydrogencarbonate solution (20 ml) then extracted with ethyl acetate (2 x 75 ml). The combined organic fractions were washed with brine (40 ml), dried over anhydrous sodium sulfate and evaporated to give a black oil. The oil was purified by silica gel chromatography eluting with dichloromethane and 1% 0.88 ammonia on a gradient of methanol (1-2%). The solid obtained was triturated with diethyl ether which gave 3'-

(imidazo[1,2-*a*]pyrazin-3-yl)biphenyl-2-carbonitrile (83 mg, 37%) as a white powder:  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.52 (1H, td, *J* 8 and 1), 7.58 (1H, dd, *J* 8 and 1), 7.61-7.74 (4H, m), 7.80-7.85 (2H, m), 7.94-7.97 (2H, m), 8.55 (1H, d), 9.18 (1H, s).

5

CLAIMS:

1. A compound of formula I, or a salt or prodrug thereof:



5

wherein

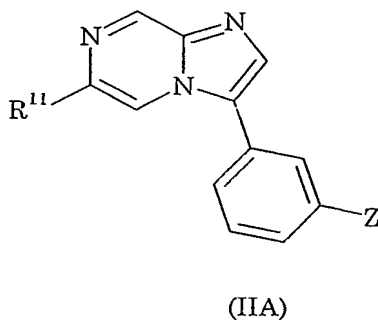
Y represents a chemical bond, an oxygen atom, or a -NH- linkage;

Z represents an optionally substituted aryl or heteroaryl group;

- 10  $R^1$  represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro,  $-OR^a$ ,  $-SR^a$ ,  $-SOR^a$ ,  $-SO_2R^a$ ,  $-SO_2NR^aR^b$ ,  $-NR^aR^b$ ,  $-NR^aCOR^b$ ,  $-NR^aCO_2R^b$ ,  $-COR^a$ ,  $-CO_2R^a$ ,  $-CONR^aR^b$  or  $-CR^a=NOR^b$ ; and

- 15  $R^a$  and  $R^b$  independently represent hydrogen, hydrocarbon or a heterocyclic group.

2. A compound as claimed in claim 1 represented by formula IIA, and salts and prodrugs thereof:



20

wherein

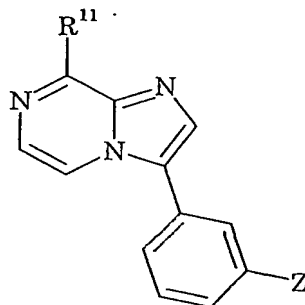
Z is as defined in claim 1;

R<sup>11</sup> represents hydrogen, C<sub>1-6</sub> alkyl, hydroxy(C<sub>1-6</sub>)alkyl, heteroaryl, halogen, trifluoromethyl, C<sub>1-6</sub> alkoxy, formyl, C<sub>2-6</sub> alkylcarbonyl, C<sub>2-6</sub> alkoxycarbonyl or -CR<sup>4</sup>=NOR<sup>5</sup>;

5 R<sup>4</sup> represents hydrogen or C<sub>1-6</sub> alkyl; and

R<sup>5</sup> represents hydrogen, C<sub>1-6</sub> alkyl, hydroxy(C<sub>1-6</sub>)alkyl or di(C<sub>1-6</sub>)alkylamino(C<sub>1-6</sub>)alkyl.

3. A compound as claimed in claim 1 represented by formula  
10 IIB, and salts and prodrugs thereof:



(IIB)

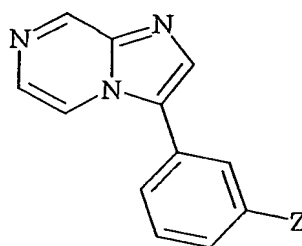
wherein

15 Z is as defined in claim 1; and

R<sup>11</sup> is as defined in claim 2.

4. A compound as claimed in claim 1 represented by formula  
IIC, and salts and prodrugs thereof:

20



(IIC)

wherein Z is as defined in claim 1.

5           5.       A compound as claimed in any one of the preceding claims  
wherein Z represents 2-cyanophenyl.

             6.       A compound selected from:  
3'-(imidazo[1,2-*a*]pyrazin-3-yl)biphenyl-2-carbonitrile;  
10       and salts and prodrugs thereof.

             7.       A pharmaceutical composition comprising a compound of  
formula I as defined in claim 1 or a pharmaceutically acceptable salt or  
prodrug thereof in association with a pharmaceutically acceptable carrier.

15

             8.       The use of a compound of formula I as defined in claim 1 or a  
pharmaceutically acceptable salt thereof or a prodrug thereof for the  
manufacture of a medicament for the treatment and/or prevention of  
anxiety.

20

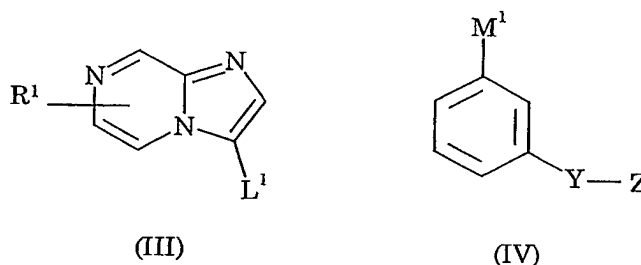
             9.       The use of a compound of formula I as defined in claim 1 or a  
pharmaceutically acceptable salt thereof or a prodrug thereof for the  
manufacture of a medicament for the treatment and/or prevention of  
convulsions.

25

10. A process for the preparation of a compound as claimed in claim 1 which comprises:

(A) reacting a compound of formula III with a compound of formula IV:

5

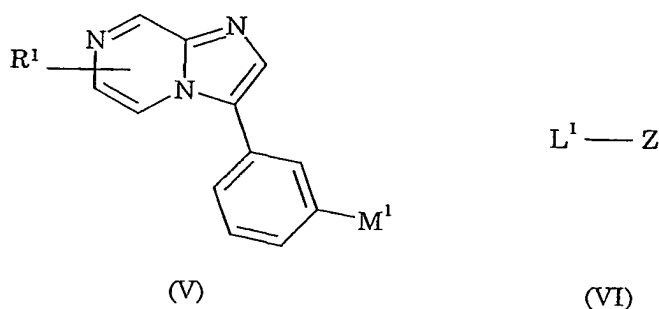


wherein Y, Z and R¹ are as defined in claim 1, L¹ represents a suitable leaving group, and M¹ represents a boronic acid moiety -B(OH)₂ or a cyclic ester thereof formed with an organic diol, or M¹ represents -Sn(Alk)₃ in which Alk represents a C₁-₆ alkyl group; in the presence of a transition metal catalyst; or

10

(B) reacting a compound of formula V with a compound of formula VI:

15

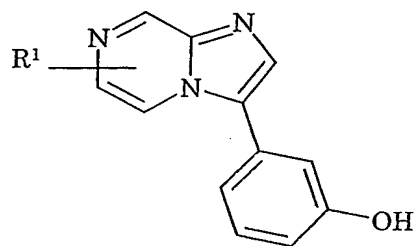


wherein Z and R¹ are as defined in claim 1, and L¹ and M¹ are as defined above; in the presence of a transition metal catalyst; or

20

(C) reacting a compound of formula VI as defined above with a compound of formula VII:

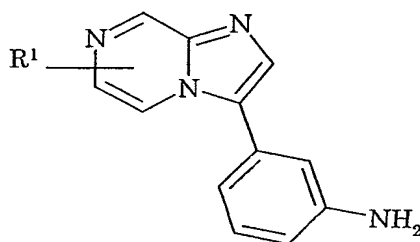




(VII)

wherein R¹ is as defined in claim 1; or

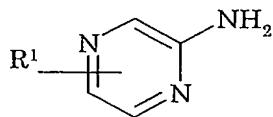
- (D) reacting a compound of formula VI as defined above with a  
5 compound of formula VIII:



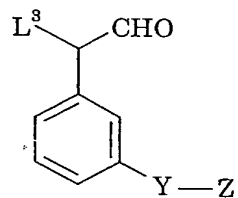
(VIII)

wherein R¹ is as defined in claim 1; or

- 10 (E) reacting a compound of formula XII with a compound of formula  
XIII:



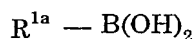
(XII)



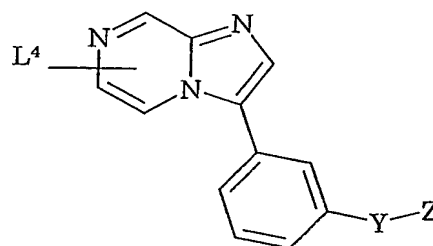
(XIII)

- 15 wherein Y, Z and R¹ are as defined in claim 1, and L³ represents a suitable  
leaving group; or

(F) reacting a compound of formula XIV with a compound of formula XV:



(XIV)



(XV)

5

wherein Y and Z are as defined in claim 1, R<sup>1a</sup> represents an aryl or heteroaryl moiety, and L<sup>4</sup> represents a suitable leaving group; in the presence of a transition metal catalyst; and

(G) subsequently, if desired, converting a compound of formula I initially obtained into a further compound of formula I by techniques known from the art.

11. A method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof.

12. A method for the treatment and/or prevention of convulsions which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable carrier thereof or a prodrug thereof.

International Application No  
PCT/GB 01/03214

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D487/04 A61K31/495 A61K31/415 A61P25/28  
//(C07D487/04,241:00,235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 22865 A (BASF AG) 13 October 1994 (1994-10-13) claims 1-6 ----	1-11
A	WO 98 04559 A (MERCK SHARP & DOHME LTD.) 5 February 1998 (1998-02-05) claims 1-23 ----	1-11
A	WO 99 37648 A (MERCK SHARP & DOHME LTD.) 20 July 1999 (1999-07-20) claims 1-9 ----- -/--	1-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

<sup>o</sup> Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

14 November 2001

Date of mailing of the international search report

22/11/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer \_\_\_\_\_

Herz, C

## INTERNATIONAL SEARCH REPORT

In

onal Application No

PCT/GB 01/03214

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>X. ZHAO, R. ZHANG: "A novel approach to the synthesis of 1-substituted-3,6-diaryl-imidazo[1,5-b]pyridazines"</p> <p>SYNTH. COMMUN., vol. 25, no. 20, 1995, pages 3271-3286, XP001033825 * Scheme 2 *</p> <p>-----</p>	1-11

## INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/GB 01/03214

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9422865	A	13-10-1994	DE 4329970 A1	06-10-1994
			AT 173263 T	15-11-1998
			AU 6428294 A	24-10-1994
			BR 9406034 A	02-01-1996
			CA 2158167 A1	13-10-1994
			CN 1120336 A ,B	10-04-1996
			CZ 9502464 A3	13-03-1996
			DE 59407285 D1	17-12-1998
			WO 9422865 A1	13-10-1994
			EP 0691970 A1	17-01-1996
			FI 954614 A	28-09-1995
			HR 940210 A1	31-12-1996
			HU 73970 A2	28-10-1996
			IL 109076 A	10-06-1997
			JP 8508271 T	03-09-1996
			NO 953892 A	29-09-1995
			NZ 263552 A	24-06-1997
			PL 310950 A1	08-01-1996
			SI 9420023 A	30-04-1996
			ZA 9402246 A	02-10-1995
WO 9804559	A	05-02-1998	AU 724076 B2	14-09-2000
			AU 3551997 A	20-02-1998
			AU 723098 B2	17-08-2000
			AU 3553997 A	20-02-1998
			BG 103112 A	30-09-1999
			BR 9710729 A	17-08-1999
			CA 2260774 A1	05-02-1998
			CN 1251589 A	26-04-2000
			CZ 9900181 A3	16-06-1999
			EE 9900027 A	16-08-1999
			EP 0915877 A1	19-05-1999
			EP 0915875 A2	19-05-1999
			WO 9804560 A1	05-02-1998
			WO 9804559 A2	05-02-1998
			JP 2000515851 T	28-11-2000
			NO 990304 A	25-03-1999
			PL 331072 A1	21-06-1999
			SK 9399 A3	10-04-2000
			TR 9900047 T2	22-03-1999
			US 6255305 B1	03-07-2001
			ZA 9706591 A	18-08-1998
			HR 980035 A1	30-06-1999
WO 9937648	A	29-07-1999	AU 2066099 A	09-08-1999
			EP 1056746 A1	06-12-2000
			WO 9937648 A1	29-07-1999
			US 6303605 B1	16-10-2001

**THIS PAGE BLANK (USPTO)**